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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,432	07/29/2003	Dennis P. Curran	96-029 CON3	6034

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/629,432	CURRAN ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/05 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicants have narrowed the claims to just two species, which were the two recited previously in claim 39. Applicants have broadened claim 14 to embrace all cancers.

Claims 14 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples;

and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Two species are covered.

(b) Scope of the diseases covered. The coverage is immense. There are hundreds and hundreds of diverse cancers, which exist in all parts of the body. Some examples:

A. Melanoma is a general type of cancer, arising from cells which produce melanin, and again is distributed fairly widely in the body, including the regional lymph nodes, skin, liver, lungs, eye, brain, and mucous membranes of the genitalia, anus, oral cavity and other sites. As an example, malignant Melanoma is a malignancy of melanocytes, and occurs most commonly in the skin, but can also appear beneath the nail plate, in the eyes, ears, GI tract, leptomeninges of the central nervous system, and oral and genital mucous membranes. There are 4 major types: superficial spreading, nodular, lentigo maligna, and acral lentiginous melanoma. There are a number of uncommon forms as well: Desmoplastic/neurotropic melanoma, Mucosal (lentiginous) melanoma, Malignant blue nevus, Melanoma arising in a giant congenital nevus, and Melanoma of soft parts (a kind of clear cell sarcoma). In addition, there are Amelanotic melanomas, which are nonpigmented.

B. There are several main types of stomach cancers, which are very different from each other. (1) Lymphomas of the stomach are cancers of the immune system tissue that are found in the wall of the stomach. These come in two main categories. One is the Non-

Hodgkin's lymphomas of the stomach, including MALT lymphoma, and assorted Large Cell Lymphoma of the Stomach such as anaplastic CD30 (Ki-1) positive large cell lymphoma (ALCL). The other is Hodgkin Lymphoma in the Stomach. These include both lymphomas which are primary to the stomach, and nodal lymphomas that have spread to the stomach from e.g. the spleen or liver and are thus secondary. There are Tertiary gastric lymphomas as well. (2) Gastric stromal tumors (GISTs) develop from the tissue of the stomach wall. There are an assortments of these; GISTs vary from cellular spindle cell tumors to epithelioid and pleomorphic ones. (3) Carcinoid tumors are tumors of hormone-producing cells of the stomach. These are classified into are classified into those that are associated with hypergastrinemic states (type 1, atrophic gastritis, pernicious anemia); Zollinger-Ellison syndrome [ZES] tumors (type 2), and tumors without hypergastrinemia (type 3 or sporadic). (4) Carcinoma of the Stomach exists in five types: papillary, tubular, mucinous, signet-ring cell adenocarcinoma and undifferentiated carcinoma. (5) Soft tissue sarcomas, most notably leiomyosarcoma of the stomach. There are other tumors as well, including Gastric Lipoma, gastric xanthelasma, and benign reactive lymphoid hyperplasia (pseudolymphoma).

C. There are many types of colon cancers, and this category is rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas, sarcomas (including fibrosarcomas and Leiomyosarcomas), and Carcinoid tumors. Because these are fundamentally different types of tumors, their treatment greatly differs, although adenocarcinomas and squamous cell tend to be treated the same.

D. Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These includes viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia (HCL, a chronic leukemia). There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias, acute promyelocytic leukemias, acute myelomonocytic leukemia, chronic myelomonocytic leukemia, acute monocytic leukemias, and erythroleukemias. There is also acute megakaryoblastic leukemia, acute promyelocytic leukemia, Multiple Myeloma, lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-/BCR- myeloid leukemia, acute basophilic leukemia, and acute myleofibrosis. Chromic leukemias include chronic lymphocytic leukemia(CLL, which exists in a B-cell and a T-cell type), prolymphocytic leukemia(PLL), large granular lymphocytic leukemia (LGLL, which goes under several other names as well), chronic myelogenous leukemia(CML), chronic myelomonocytic leukemia, chronic granulocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia and many others.

E. The main types of lung cancer are small cell (oat cell), Giant Cell Carcinoma, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, mesothelioma and Large Cell Carcinoma (a default category of any lung tumor that cannot be otherwise classified).

F. CNS cancers cover a very diverse range of cancers in many categories and subcategories. There are an immense range of neuroepithelial tumors. These include astrocytic tumors (e.g. astrocytomas and glioblastoma multiform) oligodendroglial tumors, Ependymal cell tumors (e.g. myxopapillary ependymoma), mixed gliomas (e.g. mixed oligoastrocytoma and ependymo-astrocytomas) tumors of the choroid plexus, neuronal and mixed neuronal-glial tumors (e.g. gangliocytoma, gangliogliomas, central neurocytoma, dysembryoplastic neuroepithelial tumor, esthesioneuroblastoma), pineal parenchyma tumors (e.g. pineocytoma, pineoblastoma), embryonal tumors (e.g. medulloepithelioma, neuroblastoma, retinoblastoma, ependymoblastoma) and others such as polar spongioblastoma and Gliomatosis cerebri. A second Division is tumors of the meninges. This includes tumors of the meningothelial cells, including Meningiomas (including fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, clear cell, chordoid, lymphoplasmacyte-rich, and metaplastic subtypes) and others such as papillary anaplastic meningioma. The category also includes non-meningothelial tumors of the meninges. Examples are benign mesenchymal tumors (e.g. osteocartilaginous tumors), malignant mesenchymal tumors (e.g. chondrosarcoma, hemangiopericytoma, rhabdomyosarcoma and meningeal sarcomatosis) primary pelanocytic Lesions (e.g. diffuse melanosis, melanocytoma), hemopoietic neoplasms (e.g. plasmactoma). A third Division are the tumors of Cranial and Spinal Nerves. This includes schwannomas, neurofibroma, and malignant peripheral nerve sheath tumor (MPNST). A fourth division are Germ Cell

Tumors, including germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma. A fifth division are the tumors of the Sellar Region, viz. pituitary adenoma, pituitary carcinoma and craniopharyngioma. Yet another division are local extensions from regional tumors, including paraganglioma, chodroma, chordoma, and chondrosarcoma. And there are many, many others.

G. Included also are bone tumors, including Osteosarcomas (osteoblastic, chondroblastic, fibroblastic, telangiectatic, and others), Hemangiosarcoma, Periosteal chondrosarcoma, Periosteal fibrosarcoma, Maxillary fibrosarcoma, Parosteal osteosarcoma, Periosteal osteosarcoma, Malignant mesenchymoma, Liposarcoma, synovial sarcoma, Osteochondroma, Hemangioma, Myxoma of the jaw, Ossifying fibroma, Osteoma, Giant cell tumor of bone, multiple myeloma, solitary myeloma, reticulum cell sarcoma, malignant fibrous histiocytoma, desmoblastic fibroma of the bone, periosteal fibroma, lipoma, Hemangioendothelial sarcoma, Ewing's sarcoma, chondroblastoma, and Multilobular tumor of bone. There are also secondary malignant deposits in bone.

H. Thyroid cancer comes in four forms: papillary thyroid cancer, follicular thyroid cancer, anaplastic thyroid cancer, and medullary thyroid cancer. Of these, only one (anaplastic thyroid cancer) can be treated with anticancer agents. The other are treated with radioactivity, surgery, or thyroid suppression hormones.

I. Prostate Cancer ranges over a very wide variety of cancer types. It embraces various adenocarcinomas of the prostate, including Prostatic Ductal Adenocarcinoma, adenocarcinoma with Paneth-like cells, Clear cell adenocarcinoma, Foamy gland adenocarcinoma, Adenocarcinoma of Cowper's glands, and Atrophic adenocarcinoma. It includes a huge variety of carcinomas, including s mucinous carcinomas of the prostate,

Prostatic carcinoma of xanthomatous type, signet ring cell carcinoma of the prostate, neuroendocrine small cell carcinoma of the prostate, and other small cell carcinomas of the prostate, Adenosquamous And Squamous Cell Carcinomas, Basaloid And Adenoid Cystic Carcinoma, Sarcomatoid carcinoma of the prostate, Lymphoepithelioma-like Carcinoma of the prostate, Urothelial (transitional Cell) Carcinoma (which can be primary in the prostate gland or represent secondary spread from the urinary bladder), Basaloid carcinoma, pseudohyperplastic carcinoma, and Primary carcinoma of the Seminal vesicles. There are also assorted sarcomas of the prostate, including Angiosarcoma, Embryonal rhabdomyosarcoma, Stromal sarcoma, Synovial sarcoma, Leiomyosarcoma, and chondrosarcoma of the prostate, which can be primary or secondary to the prostate. Also included is prostatic intraepithelial neoplasia (PIN), Phyllodes Tumor of the Prostate, Primitive peripheral neuroectodermal tumor (PNET) and Malignant fibrous histiocytoma. There are also lymphomas, which are usually secondary, but primary ones include Diffuse Large B-cell Lymphoma. The great majority of the above list are not treatable with pharmaceuticals.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is deficient. The daily dosage range information was omitted from the specification.

(4) State of the Prior Art: The claimed compounds are camptothecins. No camptothecin has ever been found to be effective against cancer generally.

(5) Working Examples: No actual working examples for the treatment of cancer are presented. Data appears for 3 cell lines. However, one cell line cannot possible demonstrate leukemia generally, and one cannot demonstrate lung generally, given the huge diversity of leukemias and lung cancers.

(6) Skill of those in the art: The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect just a single organ are often not generally treatable. Since it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. One skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out

many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. No compound has ever been found effective generally against leukemias, lung cancers, melanomas, etc because they are simply too diverse. Lymphomas of the stomach are not commonly treated with ordinary anti-cancer agents, but instead, surgery or radiation or antibiotic therapy(e.g. amoxicillin, metronidazole, bismuth, omeprazole) are the Primary Treatments. Treatment of malignant melanoma is normally with surgery or biological agents. Chemotherapy with non-biologics has a very limited role. The great majority of prostate cancers are not treatable with pharmaceuticals. Indeed, he majority of common cancers do not respond to chemotherapy. (7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1 and 6, the quantity of experimentation needed is expected to be great.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999

F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The traverse is unpersuasive. Applicants had previously made a broad statement about what "camptothecin analogs" do, but this is simply not true in terms of the actual scope of this claim. Where is there evidence for example that such compounds are effective against e.g. lymphomas of the stomach, squamous cell cancer of the colon, hairy cell leukemia , or mesothelioma of the lung? With regard to the dosage, applicants point to page 10, but this simply gives the size of a dose, not a daily or weekly dosage. Thus, one does not know whether this dose is to be given, say, once a week or given e.g. 4 times a day. Applicants refer in this regard to FDA approval, but the PTO is not concerned with that; merely with what the specification actually teaches.

Applicants now state that 'the claims as amended set forth the subject matter of claims 39 and 40 that the examiner indicated to be allowable". This is not so. Claims 39-40 were compound claims, these are method claims.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

Mark L. Berch

Primary Examiner

Art Unit 1624

12/29/05